EPA Reviewer: Chris Schlosser, M.F.S. **Signature**: _____
Risk Assessment Branch VI, Health Effects Division (7509P) **Date:** _____
EPA Secondary Reviewer: Elizabeth Mendez **Signature**: _____
Immediate Office (IO), Health Effects Division (7509P) **Date:** _____

Template version 09/11

TXR#: 0056765

DATA EVALUATION RECORD[1]

STUDY TYPE: Prenatal Developmental Toxicity Study - Rabbit; OPPTS 870.3700b [§83-3b]; OECD 414.

PC CODE: 016331 **DP BARCODE:** D410187

TEST MATERIAL (PURITY): Momfluorothrin (95.7% a.i.)

SYNONYMS: S-1563

CITATION: Iwashita, K. (2011). Study for Effects on Embryo-fetal Development of S-1563 Administered Orally to Rabbits. Environmental Health Science Laboratory, Osaka, Japan. Study No. 7173. March 30, 2011. MRID 49020014. Unpublished.

SPONSOR: Sumitomo Chemical Company, Ltd

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 49020014) momfluorothrin (S-1563) (95.7% a.i., batch/lot 9CM0109G) was administered to New Zealand White rabbits (24/dose) in 0.5% aqueous methylcellulose by gavage at dose levels of 0, 100, 300, or 1000 mg/kg bw/day from days through 6 through 27 of gestation.

No treatment related effects on mortality, clinical signs, body weights or gross pathology were reported. Decreases in food consumption in the absence of maternal toxicity and body weight changes were not considered to be toxicologically relevant.

The maternal NOAEL is 1000 mg/kg/day.

No significant effects were observed between the control group and treatment groups regarding the number of implantations; rate of pre-implantation loss, post-implantation loss, early resorptions, late embryonic death, and dead fetuses, number of live fetuses, sex ratio, or body weight of live male and female fetuses. No effects were observed when compared to controls on external, visceral or skeletal examinations.

The developmental NOAEL is 1000 mg/kg/day.

1 Disclaimer: The attached Data Evaluation Record is a modified version of the Tier II Summary provided by Sumitomo Chemical Co. Ltd. Portions of this document may have been altered by the EPA reviewer.

The developmental toxicity study in the rabbit is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbits.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test Material Momfluorothrin
Description: Pale yellow powder
Lot/Batch: 9CM0109G
Purity: 95.7%
CAS#: 609346-29-4
Stability: Confirmed by analysis during the study period

2. Vehicle 0.5% w/v aqueous methylcellulose

3. Test Animals
Species Rabbit
Strain New Zealand White (Kbl:NZW)
Age 19 – 22 weeks at start of dosing
Weight 3.34 – 4.34 kg at start of dosing
Source Kityama Labes, Co., Ltd, Japan
Acclimation period 14 days
Diet Pellet diet LRC4 (Oriental Yeast Co., Ltd) *ad libitum*
Water Mains water *ad libitum*
Housing Animals housed individually in suspended cages (450 x 550 x 380 (H) mm), with stainless steel grid front and floor and aluminum walls.
Environmental conditions
Temperature 21.6 – 22.8 ºC (acceptable range: 20 to 24ºC)
Humidity 43.6 – 65.4% (acceptable range: 40 to 70%)
Air change 10 air changes per hour
Photoperiod 12 hour light / dark cycle

B. PROCEDURES AND STUDY DESIGN

1. **In life dates:** 27 October 2010 – 13 April 2010

2. **Mating:** Female rabbits were artificially inseminated with semen collected from multiple males. The day of mating was designated as gestation day 0.

3. **Animal Assignment:** Animals were assigned by a weight stratification using a computer program to dose groups as indicated in Table 1.

TABLE 1: Animal Assignment

Dose (mg/kg bw/day)	0	100	300	1000
Number of Females	24	24	24	24

4. **Dose selection rationale:** The dose levels were selected based on the results from a dose range-finding study where oral administration of up to 1,000 resulted in slight suppression of

food consumption in dams. Therefore, 1,000 mg/kg was used as the high dose.

5. **Dosage preparation and analysis:** Dosing solutions were prepared at least once every two weeks. Test material-vehicle mixture was prepared by mixing appropriate amounts of test substance with methylcellulose and was stored under refrigerated conditions. Prior to the start of the study, stability of the test substance in methylcellulose was evaluated for a period of 14 days at room temperature. Concentration and homogeneity (top, middle, and bottom) of the test mixture were evaluated once during study period.

Results:
Homogeneity analysis (%RSD): 2.2 to 3.1

Stability analysis (% Initial): 101.2 to 102.6% after 14 days at 0-10 ºC

Concentration analysis (% Nominal): 99.33 to 102%

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** All doses were administered once daily by oral gavage, on gestation days 6 through 27, in a volume of 5 mL/kg of body weight/day. Dosing was based on the body weight on the most recent body weight determination.

C. OBSERVATIONS:

1. **Maternal observations and evaluations:** The animals were checked for mortality or clinical signs twice daily during treatment and once daily at all other times. Body weight and food consumption data were recorded at 3-day intervals during the gestation period. Dams were sacrificed on day 28 of gestation. Examinations at sacrifice consisted of: cervical, thoracic, and abdominal organs (including gross observation of placenta), number of corpora lutea, number of implantations, intrauterine sites of dead embryos/fetuses, timing and number of deaths, number of live fetuses, and findings of live fetuses.

   For 5 pregnant animals in the control group, the liver, kidney, spleen, heart, lung, stomach, small intestine, large intestine, thyroid gland, thymus, adrenal, ovary, and uterus were fixed and preserved in 10% neutral buffered formalin solution. Since no organ anomalies were observed in the test substance groups, they were discarded after necropsy of all animals was completed.

   Animals that aborted or prematurely delivered were, after the number of expulsed fetuses and the number of placentae were counted, euthanized rapidly and necropsied to observe the cervical, thoracic, and abdominal organs (including gross observation of placenta), the number of corpora lutea, the number of implantations, intrauterine sites of dead embryos/fetuses, timing and number of deaths, and number of live fetuses. After the observation, fetuses and placenta, in addition to thoracic and abdominal organs as performed with animals in the control group, were fixed and preserved in 10% neutral buffered formalin solution.

2. **Fetal evaluations:** Live fetuses were measured for body weight, observed for external anomalies including oral anomalies, and identified for sex based on the internal genitalia. The thoracoabdominal organs of fetuses without external anomalies were observed by necropsy. Heads from approximately half of the fetuses and the heart isolated from all fetuses were fixed in Bouin's fluid and observed. Fetuses that had been subjected to visceral observation were, after removing the brown fat in the cervical and scapular regions, fixed in dehydrating alcohol, stained with alizarin red S, and then, subjected to skeletal observation. After observation, they were preserved in glycerol solution. For approximately half of the fetuses the head of which was fixed in Bouin's fluid, skeletal examination of the head was not performed. All observations, except for the measurement of fetal body weight, were performed under blinded conditions.

D. DATA ANALYSIS:

1. **Statistical analyses:** Differences were considered significant at the 5% and 1% probability levels. Non-pregnant animals were excluded from evaluation. For fetal data, the litter was used as the unit for comparison.

   Continuous numerical data (including bodyweights, food consumption, uterine and placental weights, implantations, number of fetuses) were subject to Bartlett's test for homogeneity, then to Dunnett's test (homogeneous variances) or Steel's test (inhomogeneous variances). Pre-implantation loss, post-implantation loss, sex ratio, and numbers of fetuses with anomalies, were compared using Steel's multiple comparison test.

2. **Indices:** The following indices were calculated from cesarean section records of animals in the study: Implantation efficiency: (number of implantations/ number of corpora lutea) x 100; Rate of post-implantation loss: (number of live fetuses / number of implantations) × 100.

3. **Historical control data:** Historical control data were provided for kidney malposition malformations to allow comparison with concurrent controls.

II. RESULTS:

A. MATERNAL TOXICITY:

1. **Mortality and clinical observations:** No treatment-related effects were identified at any dose level. No mortality was observed.

2. **Body weight:** Body weight data are summarized in Table 2 and as follows: Mean body weight on each gestation day did not show any significant difference between the control group and any of test substance groups.

TABLE 2: Mean (±SD) maternal body weight gain (g) [a]

Interval	Dose in mg/kg bw/day (# of Dams)			
	Control (21)	100 (22)	300 (20)	1000 (21)
Pre-treatment: Day 0	3.70 ± 0.252	3.69 ± 0.218	3.68 ± 0.183	3.70 ± 0.191
Treatment				
Day 6	3.82 ± 0.255	3.78 ± 0.214	3.81 ± 0.171	3.82 ± 0.22
Day 9	3.83 ± 0.255	3.78 ± 0.207	3.81 ± 0.163	3.80 ± 0.230
Day 12	3.88 ± 0..260	3.80 ± 0.206	3.82 ± 0.150	3.84 ± 0.231
Day 15	3.91 ± 0.280	3.83 ± 0.232	3.83 ± 0.165	3.89 ± 0.224
Day 18	3.90 ± 0.288	3.84 ± 0.267	3.83 ± 0.167	3.88 ± 0.251
Day 21	3.91 ± 0.292	3.87 ± 0.259	3.84 ± 0.173	3.90 ± 0.254
Day 24	3.94 ± 0.297	3.91 ± 0.247	3.86 ± 0.196	3.92 ± 0.263
Day 27	4.00 ± 0.292	3.92 ± 0.264	3.91 ± 0.209	3.97 ± 0.266
Post-treatment: Day 28	4.00 ± 0.292	3.93 ± 0.269	3.92 ± 0.238	3.97 ± 0.280
Corrected BW gain[b]	-0.19 ± 0.175	-0.25 ± 0.192	-0.29 ± 0.185	-0.26 ± 0.210

[a] Data obtained from page 44-47 in the study report.
[b] Bodyweight change on Gestation Day 28 – gravid uterine weight
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

3. **Food consumption:** Significant decreases in food consumption were observed in the mid- and top- dose groups during gestation days 6-9, and in the mid-dose group on days 9-15. However, these effects were not considered to be toxicologically relevant as there was no dose-response relationship and no effects on overall body weights or body weight gain reported.

4. **Gross pathology:** No treatment-related effects were observed.

5. **Cesarean section data:** Cesarean data are reported in Table 3 below. No significant differences were found in fetal deaths, number of corpora lutea, number of implantations, rate of implantation, number of live fetuses, or gravid uterine weight when compared to controls. A low sex ratio was observed in the 100 mg/kg group but there was no dose-response relationship and it was therefore not considered to be treatment-related.

TABLE 3: Cesarean section observations [a]

Observation	Dose (mg/kg bw/day)			
	0	100	300	1000
No. Animals assigned (mated)	24	24	24	24
No. Animals pregnant	22	22	20	21
No. Nonpregnant	2	2	4	3
Maternal wastage				
No. Aborted/Premature	2	1	1	1
Total No. corpora lutea **Mean** ± s.d.	213 (10.7 ± 2.39)	234 (11.1 ± 1.42)	206 (10.8 ± 2.41)	204 (10.2 ± 1.36)
Total No. implantations **Mean** ± s.d.	164 (8.2 ± 3.93)	184 (8.8 ± 2.83)	182 (9.6 ± 1.64)	177 (8.9 ± 2.39)
Total No. litters	20	21	19	20
Total No. live fetuses **Mean** ± s.d.	153 (7.7 ± 3.62)	166 (7.9 ± 2.74)	168 (8.8 ± 2.06)	170 (8.5 ± 2.67)
Total No. dead fetuses	11	18	14	7
Mean fetal weight (g)				
Males	36.3 ± 5.98	33.4 ± 5.51	31.4 ± 6.04*	34.7 ± 5.35
Females	33.9 ± 5.59	33.4 ± 5.57	31.5 ± 5.37	33.9 ± 5.07
Sex ratio (% male)	56	41*	47	51

[a] Data obtained from pages 50 and 51 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

B. DEVELOPMENTAL TOXICITY:

1. **External examination**: No treatment related effects were identified when compared to controls.

2. **Visceral examination:** No treatment related effects were identified when compared to controls.

3. **Skeletal examination:** No treatment related effects were identified when compared to controls.

TABLE 4a: External examinations [a]

Observations	Dose (mg/kg bw/day)			
	0	100	300	1000
No. Fetuses (litters) examined	153	166	168	170
No. Fetuses (litters) affected	0	1	1	0
Open Eye	0	1	0	0
Local edema	0	0	1	0

[a] Data obtained from pages 52 and 53 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

TABLE 4b: Visceral examinations [a]

Observations [b]	Dose (mg/kg bw/day)			
	0	100	300	1000
No. Fetuses(litters) examined	153	165	167	170
No. Fetuses with malformations	4	4	3	3
No. Fetuses with variations	68	70	77	81

[a] Data obtained from pages 70-77 in the study report.
[b] Some observations may be grouped together.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

TABLE 4c: Skeletal examinations [a]

Observations [b]	Dose (mg/kg bw/day)			
	0	100	300	1000
No. Fetuses(litters) examined	153	165	167	170
No. Fetuses with malformations	9	5	5	1
No. Fetuses with variations	109	109	128	124

[a] Data obtained from pages 54-66 in the study report.
[b] Some observations may be grouped together.
[c] Fetal (litter) incidence
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: As part of studies to evaluate the safety of S-1563, the compound was administered by gavage to pregnant rabbits from gestation days 6 to 27 corresponding to the period from fetal organogenesis to late gestation period to evaluate the effect on pregnant animals and on embryo-fetal development. As a result, decreased food consumption accompanied by suppression in body weight gain was observed in dams of the 300 mg/kg and higher dose groups. The no observed adverse effect level in dams was estimated to be 100 mg/kg in terms of maternal toxicity. Neither lethal or teratogenic effect on embryos or fetuses nor effect on the development of fetuses was observed. Thus, the no observed adverse effect level in the offspring was estimated to be 1000 mg/kg.

B. REVIEWER COMMENTS: No significant decreases in body weights or body weights gain were observed when compared to control for any of the treated groups. Additionally, no embryo-fetal toxicity was observed at any dose. Therefore, decreased food consumption observed at the mid- and high-dose was not considered to be toxicologically relevant. The maternal and fetal NOAELS are 1000 mg/kg/day.

C. STUDY DEFICIENCIES: None